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# Rationale and design of the randomized, controlled Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis (EVOLVED) trial

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**Background** The optimal timing of aortic valve replacement in asymptomatic patients with aortic stenosis is uncertain. Replacement fibrosis, as assessed by midwall (nonischemic) late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging, is an irreversible marker of left ventricular decompensation in aortic stenosis. Once established, it progresses rapidly and is associated with poor long-term prognosis in a dose-dependent manner.

**Trial design** The objective of this multicenter prospective randomized controlled trial is to determine whether early aortic valve replacement in asymptomatic patients with severe aortic stenosis can improve the adverse prognosis associated with midwall LGE. Patients will be screened for likelihood of having LGE with electrocardiography or high-sensitivity troponin I. Those at high risk will proceed to CMR imaging. Approximately 400 patients with midwall LGE will be randomized 1:1 to early valve replacement or routine care. Those who do not exhibit midwall LGE will continue with routine care and be randomized to a study registry or no further follow-up. Follow-up will be annual for approximately 3 years until the number of required outcome events is achieved. The primary endpoint is a composite of all-cause mortality and unplanned aortic stenosis-related hospitalization. The expected event rate is 25.0% in the routine care arm and 13.4% in the early intervention arm over the first 2 years; 88 observed primary outcome events will give 90% power at 5% significance level. Key secondary endpoints include all-cause mortality, sudden cardiac death, stroke, and symptomatic status.

**Conclusion** The EVOLVED trial is the first multicenter randomized controlled trial to compare early aortic valve replacement to routine care in asymptomatic patients with severe aortic stenosis and midwall LGE. (Am Heart J 2019;212:91-100.)

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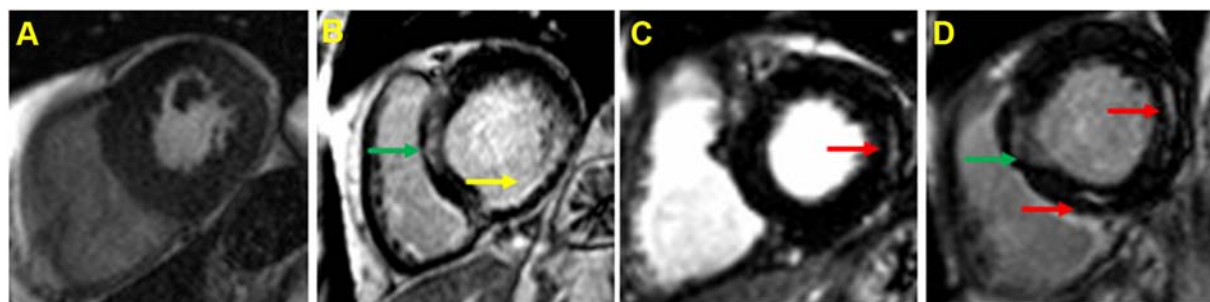
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Aortic stenosis (AS) is one of the most common valvular heart diseases in the developed world and the most common reason for valve intervention.<sup>1</sup> The prevalence has been estimated to be 12.4% in patients  $\geq 75$  years of age<sup>2</sup> and is set to treble by 2050 as a consequence of an aging population. It is characterized by progressive valve narrowing and the subsequent left ventricular remodeling response.<sup>3</sup> The only effective treatment for severe AS remains aortic valve replacement (AVR). Advances in transcatheter aortic valve replacement (TAVR) have seen an exponential rise in eligible patients, with approximately 180,000 patients across the European Union and North America meeting current criteria.<sup>4</sup>

The prognosis of symptomatic severe AS is universally recognized to be poor. Fifty years ago, Braunwald published his landmark article based on observational evidence that still influences practice today, demonstrating the association between hallmark symptom—chest pain,

**Figure 1**

Cardiac magnetic resonance in AS. **A**, Myocardium without late gadolinium enhancement. **B**, Partial voluming of the left ventricular outflow tract (green arrow) and ischemic late gadolinium enhancement (yellow arrow). **C** and **D**, Midwall late gadolinium enhancement (red arrows). **D**, Two sites of midwall late gadolinium enhancement (red arrows) and partial voluming of the left ventricular outflow tract (green arrow).

dyspnea with heart failure, and exertional syncope—and poor outcomes.<sup>5</sup> Guidelines strongly recommend AVR after the development of symptoms or a reduction in ejection fraction in the absence of symptoms<sup>6-8</sup> but rely largely on nonrandomized data and expert opinion. Symptoms are ideally used as a marker of incipient left ventricular decompensation prior to the onset of heart failure or irreversible myocardial injury. In modern clinical practice, however, the assessment of symptoms is challenging, particularly in elderly patients who may be frail, be less mobile, or have multiple comorbidities. These patients are vastly more common than 50 years ago. Meanwhile, reduced ejection fraction is frequently a late finding and often irreversible. Consequently, there is interest in developing novel, objective markers of early ventricular decompensation due to progressive valvular obstruction.

Myocardial fibrosis is the key pathological feature driving left ventricular decompensation in AS and the transition from hypertrophy to heart failure.<sup>9,10</sup> It can be divided into diffuse fibrosis, which occurs earlier and is reversible, and replacement fibrosis, which occurs later and is irreversible.<sup>11</sup> Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging allows direct imaging of replacement myocardial fibrosis, which occurs in a midwall (nonischemic) distribution in AS that can be clearly differentiated from prior myocardial infarction (Figure 1). LGE is a powerful predictor of adverse prognosis in a broad range of myocardial pathologies, including ischemic and nonischemic cardiomyopathies and infiltrative disease processes.<sup>12-16</sup> LGE is an independent predictor of mortality in patients with AS (Figure 2); this has been a consistent finding in multiple separate cohorts and multicenter studies.<sup>17-21</sup> Furthermore, once established, replacement fibrosis progresses rapidly and does not regress after AVR.<sup>11,22</sup> This is of clinical importance because a proportionate effect on clinical outcomes has been demonstrated: the more LGE, the worse the long-term prognosis.<sup>21</sup> On the basis of

these data, there is substantial interest in using midwall LGE as an early marker of left ventricular decompensation that can be used to trigger AVR in patients with asymptomatic severe AS.

## Hypothesis

We hypothesize that in asymptomatic patients with severe AS and midwall LGE, early AVR will improve outcomes when compared to the current standard of care.

## Methods

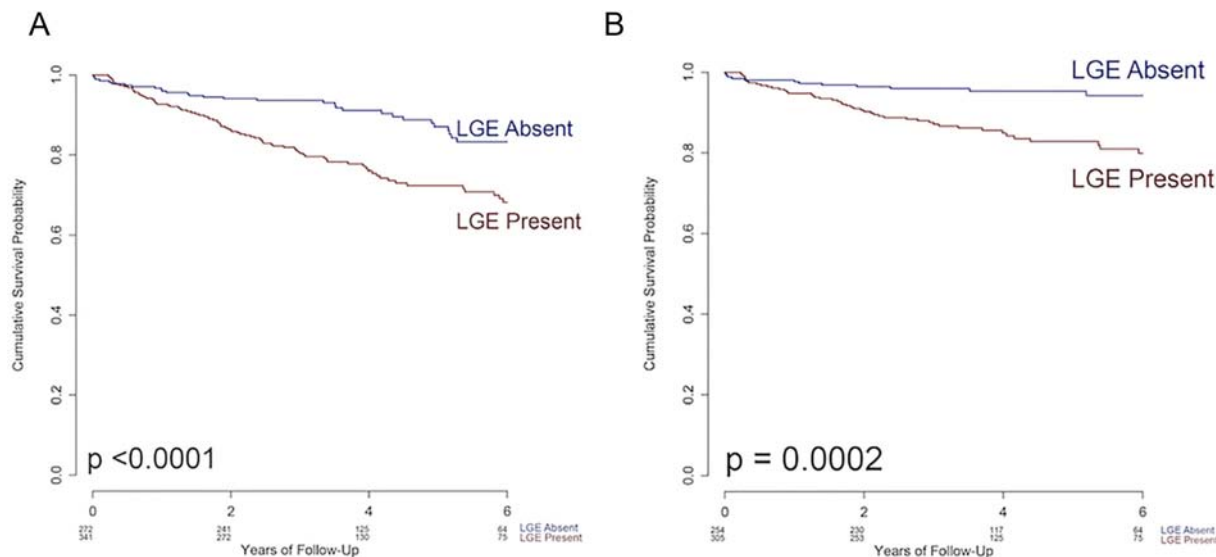
### Study design

**Setting.** The EVOLVED trial (NCT03094143) is a parallel-group, multicenter, prospective randomized open-labeled blinded endpoint controlled trial. Currently, 16 sites in the United Kingdom are recruiting; the addition of up to 15 further sites is anticipated.

**Patient population.** The trial will recruit patients >18 years of age who have severe AS and do not have symptoms attributable to their valve disease (Figure 3).

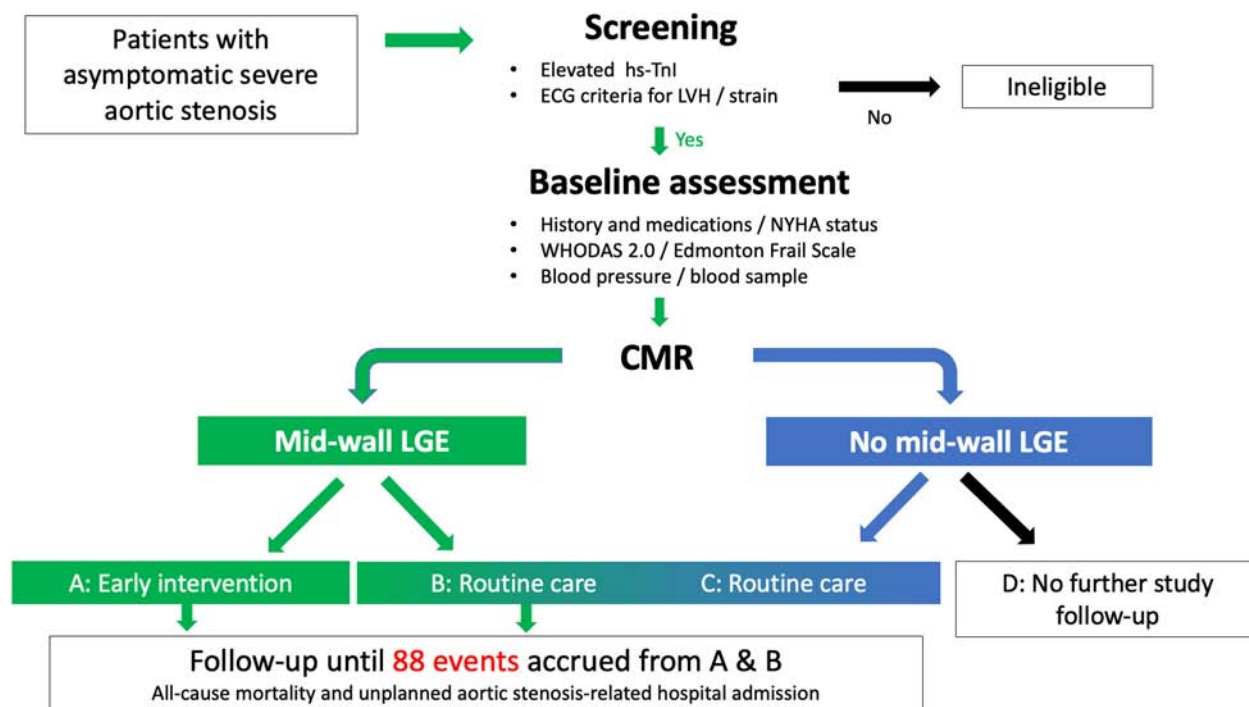
Symptoms will be assessed clinically by the attending physician; this may include exercise stress testing according to their usual clinical practice. Severe AS will be determined by the attending physician according to current guidelines, and the following echocardiographic criteria will need to be met: aortic valve peak velocity  $\geq 4.0$  m/s, or an aortic valve peak velocity  $\geq 3.5$  m/s with an indexed aortic valve area  $< 0.6$  cm<sup>2</sup>/m<sup>2</sup>.<sup>6,23</sup> Echocardiography must be performed within 6 months of the baseline visit assessment. Minimum echocardiographic parameters required for eligibility are aortic valve peak velocity, mean aortic valve gradient, aortic valve area calculated using the continuity equation, and a qualitative or quantitative assessment of left ventricular systolic function. Key exclusion criteria include left ventricular ejection fraction  $< 50\%$ , concomitant severe aortic or mitral regurgitation, estimated glomerular filtration rate

**Figure 2**



Late gadolinium enhancement and all-cause and cardiovascular mortality. Kaplan-Meier curves demonstrating the association between late gadolinium enhancement on cardiac magnetic resonance and all-cause (A) and cardiovascular (B) mortality in patients with severe AS. Figures from Musa et al.<sup>21</sup>

**Figure 3**



Study flowchart. The sample size has been calculated based on an event rate of 25.0% in the routine care arm and 13.4% in the early intervention arm over the first 2 years; 88 observed primary outcome events will give 90% power at 5% significance level.

**Table I.** Inclusion and exclusion criteria

## Inclusion criteria

1. Severe AS  
AV Vmax  $\geq 4.0$  m/s, **or**  
AV Vmax  $\geq 3.5$  m/s + AVA  $< 0.6$  cm<sup>2</sup>/m<sup>2</sup>
2. No symptoms attributable to AS that warrant AVR
3.  $> 18$  years of age

## Exclusion criteria

1. Low risk for midwall fibrosis on screening
2. Planned cardiac surgery
3. Previous valve replacement
4. Severe hypertension (SBP  $> 180$  or DBP  $> 110$  mm Hg)
5. Acute pulmonary edema or cardiogenic shock
6. Left ventricular ejection fraction  $< 50\%$  on CMR
7. Significant abnormalities on CMR that would prevent enrolment
8. Coexistent severe aortic or mitral regurgitation
9. Coexistent mitral stenosis greater than mild in severity
10. Coexistent hypertrophic cardiomyopathy or cardiac amyloidosis
11. Contraindication to CMR
12. Advanced renal impairment (eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>)
13. Pregnancy or breast feeding
14. Judged to be unfit for SAVR/TAVR
15. Patient declines to consider SAVR/TAVR
16. Inability to give informed consent
17. Previous randomization into this study

AS, aortic stenosis; AV Vmax, aortic valve peak velocity; AVA, aortic valve area; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SAVR, surgical aortic valve replacement.

$< 30$  mL/min/1.73 m<sup>2</sup>, and contraindications to CMR. A full list of inclusion and exclusion criteria is provided in Table I.

**Clinical assessment and screening.** Patients will be approached and consented for a screening visit where an electrocardiogram (ECG) will be performed and plasma high-sensitivity cardiac troponin I (hsTnI) concentrations measured. Patients will proceed to baseline visit and CMR if there is ECG evidence of left ventricular hypertrophy with strain or an hsTnI concentration  $\geq 6$  ng/L. These criteria are based on prior observational data demonstrating the sensitivity and specificity of ECG evidence of left ventricular hypertrophy and/or strain for the presence of midwall LGE in patients with AS to be 88% and 67% respectively, whereas the median hsTnI in AS patients with midwall LGE was 9.5 ng/L (interquartile range [IQR] 5.7–20.3) versus 4.3 ng/L (IQR 3.3–7.9) in those without.<sup>24,25</sup> Any ECG criteria for left ventricular hypertrophy may be used, including the Peguero-Lo Presti criteria, Sokolow-Lyon index, and Cornell criteria.<sup>26–28</sup> The Abbott ARCHITECT<sub>STAT</sub> troponin I assay (Abbott Laboratories, Abbott Park, IL) will be used for plasma hsTnI measurement. At sites where access to this assay is not available, an ECG-only screening pathway will be permitted.<sup>24</sup> Other data collected at the screening visit will include relevant medical history, height and weight, blood pressure, New York Heart Association (NYHA) functional classification, Edmonton Frail Scale,<sup>29</sup> and World Health Organization Disability Assessment Schedule 2.0 (WHO-DAS).<sup>30</sup> In addition to hsTnI, further optional phlebotomy

will be performed and the sample spun and frozen below  $-70^{\circ}\text{C}$  for future analysis. Explicit consent will be sought for these samples. Patients will also be consented at the screening visit for future data linkage analysis, regardless of whether they fulfill criteria to proceed to CMR.

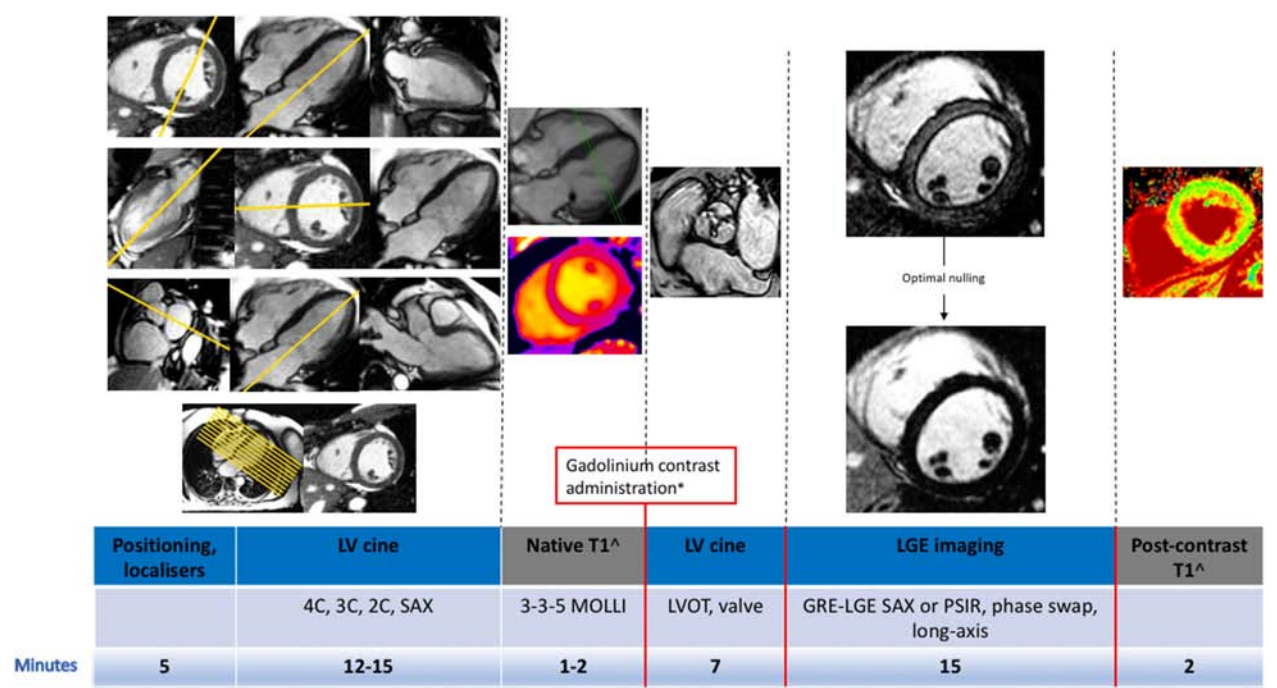
**Cardiac magnetic resonance imaging.** For CMR imaging, either a 1.5- or 3-T scanner may be used according to local availability. A standardized protocol will be applied (Figure 4), incorporating routine localizer sequences, left ventricular 2-, 3-, and 4-chamber cine imaging and a left ventricular short axis stack (8-mm slices, no gap). Native T1 measurements may be performed at the discretion of each site using the modified Look-Locker inversion recovery sequence.<sup>31</sup> A gadolinium-based contrast medium will then be administered according to local protocol; the preferred agent and dose are 0.15 mmol/kg gadobutrol. This will be followed by left ventricular outflow tract imaging and fast low angle shot sequences of the aortic valve in short axis. LGE imaging will begin 7 minutes after contrast administration and be performed using either gradient echo or phase-sensitive inversion recovery techniques, according to local practice, with a phase swap short-axis stack also acquired to help exclude artifact. Finally, postcontrast T1 measurements may be performed approximately 20 minutes after gadolinium administration. Other CMR imaging sequences of interest may also be added to the protocol where available. The images will be anonymized and uploaded to the secure EVOLVED server hosted by the University of Edinburgh for central core analysis.

The core laboratory is based at the Edinburgh Imaging Facility, Queen's Medical Research Institute, University of Edinburgh. Image analysis will be performed using cvi<sup>42</sup> for Cardiac MRI (Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Qualitative assessment of LGE will be undertaken visually; the presence or absence of a midwall pattern of LGE will be reported as a dichotomous finding for the purposes of randomization. Quantification of LGE will not be undertaken as part of primary image analysis. The presence of LGE in an ischemic pattern will be documented during image analysis, but only midwall LGE will qualify participants for randomization. In the presence of an ambiguous distribution of LGE, other findings such as regional wall motion abnormalities, segmental distribution, and myocardial thinning will be used to aid in differentiating midwall from ischemic LGE. The clinical care team is blinded to cardiac findings from the CMR, with the exception of any clinically relevant findings that would prevent enrolment or influence patient management. Such findings include, but are not limited to, left ventricular ejection fraction  $< 50\%$ , intracardiac thrombus, or malignancy.

**Randomization and blinding.** Following completion of baseline assessments, CMR imaging, and central CMR review, patients that meet inclusion and exclusion criteria will be enrolled into the study. A Web-based



**Figure 4**



Cardiac magnetic resonance protocol. The EVOLVED CMR scanning protocol with representative images from different sequences. \* The preferred gadolinium-based contrast agent and dose are gadobutrol 0.15 mmol/kg. <sup>^</sup> Pre- and postcontrast T1 imaging is optional. LV, left ventricular; 4C, 4-chamber; 3C, 3-chamber; 2C, 2-chamber; SAX, short axis; MOLLI, modified Look-Locker inversion recovery; GRE, gradient echo; PSIR, phase sensitive inversion recovery.

computer-generated randomization process will be used. To maintain blinding, there are 2 separate randomizations: one for patients with midwall fibrosis (randomization 1) and another for those without midwall fibrosis (randomization 2) (Figure 3). The 2 randomizations are critical and result in a pooled group of patients with and without midwall fibrosis who are allocated to routine care (group B/C), thus maintaining blinding in the control group (group B). This will ensure that the CMR result in the routine care group does not influence symptoms or decisions regarding timing of AVR.

For randomization 1, patients are randomized in a 1:1 ratio to either early intervention (group A) or routine clinical care (group B). Minimization techniques will be used to ensure balancing of key variables: age, sex, aortic valve peak velocity, ischemic heart disease, and screening method (ECG and hsTnI or ECG only). For randomization 2, patients will be randomized using a flexible adaptive ratio to either routine clinical care (group C) or no further study follow-up (group D). The aim of the randomization ratio, which will be undertaken by the Clinical Trials Unit, is to balance the number of participants in group C and group B. Details of the randomization ratio value and the dates of any change in the ratio will be recorded. No minimization criteria will be applied to this randomization because the primary analysis does not involve group C.

Patients who are randomized to early AVR (group A) will be referred immediately following randomization. The usual local clinical pathway will be followed; decisions such as revascularization and AVR modality (surgical or transcatheter) will be made according to the local heart valve team on a per patient basis. The intervention should be performed as soon as possible as an elective procedure and ideally within 2 months of randomization.

Follow-up for groups A, B, and C will be identical, which will maintain blinding for patients undergoing routine care (groups B and C). Patients will be telephoned annually to assess symptoms and events. NYHA functional class and WHODAS 2.0 will be assessed. Medical records will also be reviewed annually to assess for any events. Postoperative complications occurring within 30 days of surgery will be recorded, irrespective of treatment group (Supplementary Table D). Patients in Group D will not undergo any routine study follow-up, but patient details will be retained for future linkage analysis.

**Funding and contributors.** The EVOLVED trial is funded by a grant from the Sir Jules Thorn Charitable Trust (15/JTA). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

**Table II.** Study endpoints**Primary endpoint**

Composite of all-cause mortality or unplanned AS-related hospitalization between randomization and final follow-up visit for study participants with midwall fibrosis.

**Secondary endpoints**

1. Mortality (all-cause, cardiovascular, AS related, and sudden cardiac death) between randomization and final follow-up visit.
2. Unplanned AS-related hospitalization between randomization and final follow-up visit.
3. Health and disability as assessed by the 12-item WHODAS 2.0 at the final follow-up visit.
4. The development of left ventricular systolic dysfunction (ejection fraction <45% quantitatively or at least moderate left ventricular systolic dysfunction qualitatively) between randomization and final follow-up visit.
5. Symptomatic status as assessed by NYHA functional classification at the final follow-up visit.
6. Permanent pacemaker insertion, cardiac resynchronization therapy, or automated implantable cardioverter/defibrillator between randomization and final follow-up visit.
7. Stroke between randomization and follow-up visit.
8. Endocarditis between randomization and final follow-up visit.
9. 30-d postoperative complications following aortic valve intervention

**Endpoints**

The primary endpoint is a composite endpoint of all-cause mortality and unplanned AS-related hospitalization between randomization and final follow-up visit for study participants with midwall fibrosis (groups A and B). *Unplanned AS-related hospitalization* is defined as an unplanned hospital admission with syncope, heart failure, chest pain, or arrhythmia (ventricular arrhythmia or second- or third-degree heart block) attributed to AS. This endpoint will be independently adjudicated by 2 investigators blinded to the details of randomization. AS-related hospitalizations occurring in the early intervention arm between randomization and intervention will be included in the intention-to-treat analysis. A third independent reviewer will adjudicate any conflicts. There are a number of prespecified secondary endpoints (Table II, definitions in Supplementary Table II), including all-cause mortality, cardiovascular mortality, and AS-related mortality which will be analyzed in groups A, B, and C.

Other data will be collected for exploratory analysis. These will include assessment of other CMR parameters such as ejection fraction and T1 mapping (native T1, extracellular volume fraction, and indexed extracellular volume), biochemical biomarkers such as brain natriuretic peptide, and genetic analyses to assess for gene associations with myocardial fibrosis.

**Statistical considerations**

**Sample size.** We expect the proportion of primary outcome events (all-cause mortality or unplanned AS-related hospitalization) to be 25% in the routine care arm of the study and 13.4% in the early intervention arm (a hazard ratio of 2) over 2 years of follow-up.<sup>17-19</sup> Using a log-rank approach, we will need to observe 88 primary outcome events to give us 90% power at 5% significance level. We have estimated that we will reach 88 events when we have recruited 356 participants with midwall fibrosis (slightly more allowing for a 10% dropout rate) after a mean follow-up of 2.75 years. However, if

necessary, the study will continue until the prespecified number of events has accrued.

For further calculations, we have assumed that our optimal hsTnI threshold will be ~6 ng/L. This is based upon our preliminary troponin data to date, which demonstrated that 62% of patients with an aortic valve peak velocity  $\geq 4.0$  m/s had a troponin  $\geq 6.0$  ng/L. Of these patients, 42% had midwall fibrosis on CMR. On this basis, we have estimated that we will need to screen approximately 1,600 patients to identify 1,000 patients for CMR to recruit our target of 400 patients with midwall fibrosis.

At the time that the required amount of data for the primary analysis has accrued (comparing early surgery vs routine care in patients with midwall fibrosis [groups A and B]), we should also have 90% power to detect a difference in the all-cause mortality between patients with and without midwall fibrosis who do not receive early surgery (groups B and C) of 29% versus 15% (log-rank test,  $P = .05$ , 2-sided test).

**Statistical analyses.** The primary outcome is defined as time to first event of all-cause mortality or unplanned AS-related hospital admission, and the primary comparison will be between group A and group B. *Time to primary outcome* is defined as time from randomization to primary outcome. Patients withdrawing consent will have their time to primary outcome censored at the last contact date. The relationship between intervention and the primary outcome will be analyzed using Cox proportional-hazard regression adjusted for the minimization variables used in the randomization algorithm. The results will be expressed as a hazard ratio with the corresponding 95% CIs and 2-sided  $P$  value (which will be considered statistically significant if it is  $\leq .05$ ). The individual elements of the composite primary outcome will be reported separately.

Secondary outcomes will be analyzed using appropriate methods: Cox proportional-hazards regression for time-to-event outcomes, logistic regression for binary outcomes, and linear regression for normally distributed

continuous outcomes, adjusted as described above. Continuous outcomes that are not normally distributed will be analyzed using appropriate nonparametric techniques. Secondary outcomes will be presented for groups A, B, and C. A first set of secondary analyses will compare groups A and B, and a second set of secondary analyses will compare groups B and C.

For the purpose of analysis, we will retain participants in the treatment groups to which they were originally assigned irrespective of the treatment actually received. Every effort will be made to minimize missing data. Analysis will be a complete case analysis. If there is a sufficient level of missing data to affect our conclusions, a multiple imputation analysis will be undertaken, using clinically appropriate variables, as a sensitivity analysis. A full statistical analysis plan will be written during the trial and finalized prior to database lock.

### Ethical considerations

The study protocol will be approved by each region and will be conducted in accordance with the principles of Good Clinical Practice. The trial received a favorable ethical opinion from the South East Scotland Research Ethics Committee on 12 May 2017 (REC 17/SS/0052).

A trial steering committee will oversee the study. The former will have final responsibility for the medical and scientific conduct of the trial, while all staff must comply with the requirements of the UK Data Protection Act 2018 and the EU General Data Protection Regulation 2018. The principal investigators are responsible for the overall conduct of the study at each site. The chief investigator and trial manager are based at the Centre for Cardiovascular Science, University of Edinburgh.

Participants will be provided with oral and written information. Participants must have at least 24 hours to consider the written information before written informed consent for the main trial can be sought. Patients are free to withdraw at any stage of the trial. Any data collected until this point will be retained and analyzed unless the participant specifically withdraws consent for this. Documentation and review of any adverse events or adverse reactions that occur are the responsibility of site investigators. Only serious adverse reactions or suspected unexpected serious adverse reactions related to gadolinium-based contrast medium administration are required to be reported to the sponsor. Such an event should be reported within 24 hours.

### Current status

The main site opened on 21 July 2017, and the first patient was recruited on 16 October 2017. Subsequently, 16 other sites have opened across the United Kingdom. As of December 2018, a total of 101 patients have undergone CMR and randomization. We anticipate opening a further 10-15 sites within the next year.

After the first year of recruitment, the number of patients being screened has been lower than expected. However, the anticipated prevalence of midwall fibrosis in patients who have proceeded to CMR has exceeded the anticipated rate of approximately 40%. Given this, as well as the new sites yet to open, the trial remains on course to reach the expected event rate (88 primary outcome events). Additionally, the reduced number of CMR scans that are likely to be required, given the observed prevalence of midwall fibrosis, provides flexibility with resource allocation, with the provision of extending study follow-up available as a viable option.

### Trial registration

The EVOLVED trial is registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03094143) (NCT03094143).

### Funding

The EVOLVED trial is supported by a grant from the Sir Jules Thorn Charitable Trust (15/JTA).

## Discussion

The optimal timing of aortic valve replacement in patients with severe AS remains unclear, having never been investigated in the context of a randomized controlled trial. Current major international guidelines support the consideration of intervention in asymptomatic patients if there is very severe AS or rapid progression in valve obstruction, whereas additional weaker recommendations are offered by the European Society of Cardiology based on severe pulmonary hypertension or elevated brain natriuretic peptide attributable to AS.<sup>6-8</sup> However, long-term outcomes after AVR remain suboptimal. A growing body of data has identified midwall LGE to be a powerful independent predictor of poor prognosis under the current management paradigm. This has recently been confirmed in a large multicenter cohort, comprising almost 700 patients (all-cause mortality 25.2% vs 12.9% at median 3.6 years of follow-up for patients with and without LGE, respectively).<sup>21</sup> EVOLVED will investigate whether the adverse prognosis observed in these patients can be improved with early valve intervention.

Myocardial fibrosis is recognized to be the structural correlate of heart failure and is present in the later stages of most myocardial pathologies.<sup>10</sup> In AS, fibrosis appears to be the central pathological process driving left ventricular decompensation and the transition from hypertrophy to heart failure.<sup>10</sup> Myocardial fibrosis is therefore a potential biomarker for early left ventricular decompensation. LGE on CMR is well suited to the purpose of identifying replacement fibrosis. The technique can discriminate between various patterns of fibrosis, differentiating midwall fibrosis due to AS from other forms of myocardial injury such as myocardial infarction. This is an important



advantage over other parameters such as ejection fraction, diastolic dysfunction, or global longitudinal strain. Midwall LGE has been validated against histology and consistently demonstrates a close association with other markers of LV decompensation, including advanced left ventricular hypertrophy, markers of myocardial injury, reductions in diastolic and systolic ventricular function, increased symptomatic status, and reduced exercise capacity.<sup>20,32</sup> Moreover, the adverse long-term prognosis associated with midwall LGE has now been confirmed in 5 separate cohorts.<sup>17-21</sup> LGE has therefore been extensively studied with regard to prognosis; attention is now turned toward clinical application.

EVOLVED is the first randomized controlled trial to use midwall LGE as a biomarker of early left ventricular decompensation and a trigger for AVR in an asymptomatic population who does not meet conventional criteria for intervention. Our hypothesis is that prompt intervention will halt the accumulation of irreversible myocardial fibrosis—which confers ongoing risk of adverse outcomes even after AVR—thereby improving long-term patient prognosis. The primary analysis will compare the outcomes of patients with midwall LGE randomized to early intervention (group A) with those randomized to routine care (group B). Patients in group B will be pooled with patients who do not have midwall LGE and who are randomized to routine care (group C) via the second randomization. This facilitates blinding of patients, study investigators, and treating physicians to CMR results in this pooled group. There may be potential bias and subtraction anxiety in patients allocated to routine care if CMR results were available; blinding will minimize this. Furthermore, the study design will allow a comparison of the natural history of asymptomatic patients with and without LGE undergoing routine care and also allows for acquisition of T1 mapping data, an emerging area of interest in AS.

The use of treadmill exercise testing in AS is controversial. Although many physicians find it a useful adjuvant test to help assess a patient's symptomatic status, the data supporting treadmill testing in patients with AS are limited, and it has several important limitations in this patient population. Firstly, impaired mobility may preclude the use of treadmill or bicycle exercise testing in many AS patients, even if daily activities are not limited. Secondly, the criteria for determining a positive remain unclear (all patients will develop dyspnea at some point during a treadmill test), and symptoms that do develop may not necessarily be attributable to valvular disease. Thirdly, exercise testing may extend patients beyond their usual level of activity; in this scenario, symptoms elicited do not reflect the reality of symptoms within the sphere of day-to-day activity. As a consequence, clinical guidelines do not mandate the use of treadmill testing, and its use varies widely among practicing clinicians. Our approach to treadmill testing reflects these clinical

realities. We have not mandated the use of exercise treadmill testing as part of our study protocol; however, if physicians wish to perform a treadmill test to determine a patient's symptomatic status as part of routine care, they are free to do so; this will not affect the patient's eligibility. Ultimately, EVOLVED is envisaged as a pragmatic randomized controlled trial designed to be applicable to the broadest range of patients seen in daily clinical practice.

We have introduced a screening step before CMR to mitigate the imaging costs of our strategy, both within the trial and in future clinical practice. Estimation of plasma hsTnI concentrations now facilitates the detection of myocardial injury at extremely low levels in a range of conditions beyond myocardial infarction; consequently, normal values (approximately <6 ng/L) are a consistent predictor of patients at low risk of adverse outcome.<sup>33,34</sup> This includes AS, where hsTnI levels are associated not with markers of coronary artery disease but instead with the degree of hypertrophy and the presence of myocardial fibrosis.<sup>25</sup> As a cheap, widely available, and easily performed blood test, hsTnI is an ideal screening tool with which to select patients for CMR. The ECG strain pattern has been shown to have a high specificity for myocardial fibrosis in AS<sup>24</sup> but may be a suboptimal screening tool when used in isolation due to low sensitivity. Therefore, at those sites where the Abbott hsTnI assay is not available, voltage criteria for LVH (with or without strain) will be used instead. We expect this screening approach to reduce the number of CMR scans in the EVOLVED trial by more than one-third.

Two additional randomized controlled trials in severe asymptomatic AS are currently under way. A well-designed but small trial (AVATAR) that aims to recruit 312 patients is under way, initiated in Serbia and conducted in Europe (NCT02436655).<sup>35</sup> This study is different to EVOLVED with 17 exclusions (including coronary artery disease and chronic obstructive pulmonary disease). Additionally, all patients must be able to undergo exercise testing, and coronary angiography is mandatory; this may limit the generalizability of the results. The EARLY TAVR trial, randomizing patients with asymptomatic severe AS to expectant treatment or TAVR, commenced in July 2017 (NCT03042104). This industry-sponsored trial (Edwards Lifesciences) will differ markedly from the current study because it will not select out patients with LV decompensation and will mandate a specific valve replacement strategy. The primary endpoint is freedom from death, stroke, and unplanned cardiovascular hospitalization.

## Conclusions

Previous data have demonstrated that irreversible replacement fibrosis in AS accumulates rapidly once established and confirmed the poor prognosis associated

with its development. The EVOLVED trial is the first multicenter, blinded, randomized controlled trial to investigate early AVR compared to routine care in asymptomatic patients with severe AS and evidence of myocardial fibrosis on CMR. Our hypothesis is that early valve intervention will reduce deaths and unplanned cardiovascular hospitalization in these patients.

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## Disclosures

None.

## CRediT authorship contribution statement

Rong Bing: investigation, formal analysis, supervision, writing - original draft, writing - review and editing, visualization. Russell Everett: conceptualization, methodology, investigation, formal analysis, supervision, writing - original draft, writing - review and editing. Christopher Tuck: data curation, supervision, project administration, writing - review and editing. Scott Semple: methodology, software, investigation, writing - review and editing. Steff Lewis: methodology, formal analysis, writing - review and editing. Ronnie Harkess: software, data curation, resources. Nicholas L Mills: conceptualization, methodology, funding

acquisition. Thomas A Treibel: conceptualization, methodology, investigation. Sanjay Prasad: conceptualization, methodology, investigation, funding acquisition. John P Greenwood: conceptualization, methodology, investigation, writing - review and editing. Gerry P McCann: conceptualization, methodology, investigation, writing - review and editing. David E Newby: conceptualization, methodology, investigation, supervision, writing - review and editing, funding acquisition. Marc R Dweck: conceptualization, methodology, investigation, resources, writing - review and editing, visualization, supervision, funding acquisition.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ahj.2019.02.018>.

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